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Dated this 18th day of August, 2006

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[Title of the Invention] HALOGEN-SUBSTITUTED BENZENE DERIVATIVES

[Number of Claims] 18

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[List of the Documents]

[Item] Specification 1

[Item] Abstract 1

[Proof, requested or not] requested

[Name of Document] Specification

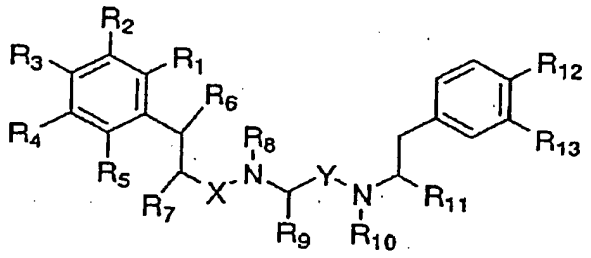
[Title of the Invention]

HALOGEN-SUBSTITUTED BENZENE DERIVATIVES

[Claims]

[Claim 1] A compound of Formula (1):

[Chemical Formula 1]



(1)

wherein:

R_1, R_2, R_3, R_4 and R_5 are hydrogen, halogen, hydroxy, or amino, and at least one of R_1, R_2, R_3, R_4 and R_5 is halogen;

R_6 is hydrogen, optionally substituted straight-chained or branched C_{1-3}alkyl, amino or hydroxy;

R_7 is hydrogen, optionally substituted straight-chained or branched C_{1-3}alkyl, optionally substituted amino or hydroxy;

R_8 is hydrogen, methyl or ethyl;

R_9 is optionally substituted straight-chained or branched C_{1-6}alkyl, C_{3-7}cycloalkyl or optionally substituted phenyl;

R_{10} is hydrogen methyl or ethyl;

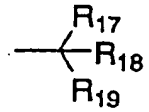
R_{11} is hydrogen, optionally substituted straight-chained or branched C_{1-3}alkyl, or $-CO-N(R_{14})R_{15}$;

R_{12} is hydroxy or $-OR_{16}$;

R_{13} is hydrogen, straight-chained or branched C_{1-6}alkyl,

straight-chained or branched C_{2-6}alkenyl, straight-chained or branched C_{2-6}alkynyl or a group of Formula (2):

[Chemical Formula 2]



(2)

R_{14} and R_{15}, which may be the same or different, are hydrogen, optionally substituted straight-chained or branched C_{1-4}alkyl, or C_{3-7}cycloalkyl, or R_{14} and R_{15}, as $-N(R_{14})R_{15}$, form optionally substituted 3- to 7-membered cyclic amine;

R_{16} is straight-chained C_{1-4}alkyl;

R_{17} is hydrogen or methyl;

R_{18} and R_{19} together form C_{3-7}cycloalkyl or C_{3-7}cycloalkenyl;

X is carbonyl or methylene;

Y is carbonyl or methylene;

or a hydrate or pharmaceutically acceptable salt thereof.

[Claim 2] The compound according to claim 1, wherein at least one of R_1, R_2, R_3, R_4 and R_5 in Formula (1) is halogen and the others are hydrogen or hydroxy;
or a hydrate or pharmaceutically acceptable salt thereof.

[Claim 3] The compound according to claim 1, wherein in Formula (1) R_3 is halogen or R_2 and R_3 are the same kind of halogen;
or a hydrate or pharmaceutically acceptable salt thereof.

[Claim 4] The compound according to claim 1, wherein in Formula (1) R_3 is halogen and R_1, R_2, R_4 and R_5

are hydrogen, or R_2 and R_3 are the same kind of halogen and R_1, R_4 and R_5 are hydrogen;
or a hydrate or pharmaceutically acceptable salt thereof.

[Claim 5] The compound according to any one of claims 1-4,
wherein R_6 in Formula (1) is hydrogen or methyl;
or a hydrate or pharmaceutically acceptable salt thereof.

[Claim 6] The compound according to any one of claims 1-5,
wherein R_7 in Formula (1) is hydrogen or optionally substituted amino;
or a hydrate or pharmaceutically acceptable salt thereof.

[Claim 7] The compound according to any one of claims 1-6,
wherein R_8 in Formula (1) is hydrogen or methyl;
or a hydrate or pharmaceutically acceptable salt thereof.

[Claim 8] The compound according to any one of claims 1-7,
wherein R_9 in Formula (1) is methyl, isopropyl, isobutyl, sec-butyl, tert-butyl, 3-pentyl, neopentyl, 1,1,1,3,3,3-hexafluoro-2-propyl, cyclohexyl, phenyl, benzyl, para-hydroxybenzyl or cyclohexylmethyl;
or a hydrate or pharmaceutically acceptable salt thereof.

[Claim 9] The compound according to any one of claims 1-8,
wherein R_{10} in Formula (1) is hydrogen or methyl;
or a hydrate or pharmaceutically acceptable salt thereof.

[Claim 10] The compound according to any one of claims

1-9,

wherein R_{11} in Formula (1) is methyl, carbamoyl, methylcarbamoyl or dimethylcarbamoyl;

or a hydrate or pharmaceutically acceptable salt thereof.

[Claim 11] The compound according to any one of claims 1-10,

wherein R_{12} in Formula (1) is hydroxy;

or a hydrate or pharmaceutically acceptable salt thereof.

[Claim 12] The compound according to any one of claims 1-11,

wherein R_{13} in Formula (1) is isopropyl, tert-butyl (tBu), 1,1-dimethylpropyl or 1,1-dimethyl-2-propenyl;

or a hydrate or pharmaceutically acceptable salt thereof.

[Claim 13] The compound according to claim 1,

wherein in Formula (1)

Cy is a group of Formula (2) in which at least one of R_1, R_2, R_3, R_4 and R_5 is halogen and the others are hydrogen or hydroxy;

R_6 is hydrogen or methyl;

R_7 is hydrogen or optionally substituted amino;

R_8 is hydrogen or methyl;

R_9 is methyl, isopropyl, isobutyl, sec-butyl, tert-butyl, 3-pentyl, neopentyl, 1,1,1,3,3,3-hexafluoro-2-propyl, cyclohexyl, phenyl, benzyl, phenethyl, para-hydroxybenzyl or cyclohexylmethyl;

R_{10} is hydrogen or methyl;

R_{11} is methyl, carbamoyl, methylcarbamoyl or dimethylcarbamoyl;

R_{12} is hydroxy;

R_{13} is isopropyl, tert-butyl (tBu), 1,1-dimethylpropyl or 1,1-dimethyl-2-propenyl;

or a hydrate or pharmaceutically acceptable salt thereof.

[Claim 14] The compound according to claim 1 which is selected from the group of compounds consisting of Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2, Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2, and Phe(3,4-F_2)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2; or a hydrate or pharmaceutically acceptable salt thereof.

[Claim 15] A medicine containing the compound according to any one of claims 1-14 as an active ingredient

[Claim 16] A motilin receptor antagonist containing the compound according to any one of claims 1-14.

[Claim 17] A gastrointestinal motility suppressor agent containing the compound according to any one of claims 1-14 as an active ingredient.

[Claim 18] A therapeutic of hypermotilinemia containing the compound according to any one of claims 1-14 as an active ingredient.

[Detailed Description of the Invention]

[0001]

[Technical Field of the Invention]

This invention relates to halogen-substituted benzene derivatives that function as a motilin receptor antagonist and that are useful as medicines.

[0002]

[Prior Art]

Motilin, which is one of the gastrointestinal

hormones, is a straight-chained peptide consisting of 22 amino acids and is well known to be responsible for regulating the motility of the gastrointestinal tract in animals including human. It has been reported that exogenously administered motilin causes contractions in humans and dogs that are similar to interdigestive migrating contractions, thus promoting gastric emptying (Itoh et al., Scand. J. Gastroenterol., 11, 93-110 (1976); Peeters et al., Gastroenterology 102, 97-101 (1992)). Hence, erythromycin derivatives which are an agonist of motilin are under development as an gastrointestinal tract motor activity enhancer (Satoh et al., J. Pharmacol. Exp. Therap., 271, 574-579 (1994); Lartey et al., J. Med. Chem., 38, 1793-1798 (1995); Drug of the Future, 19, 910-912 (1994)).

[0003]

Peptide and polypeptide derivatives have been reported as antagonists of motilin receptors (Depoortere et al., Eur. J. Pharmacol., 286, 241-247 (1995); Poitras et al., Biochem. Biophys. Res. Commun., 205, 449-454 (1994); Takanashi et al., J. Pharmacol. Exp. Ther., 273, 624-628 (1995)). These derivatives are used as a pharmacological tool in the study of the action of motilin on the motility of the gastrointestinal tract and in the research and development of medicines in the field of the art contemplated by the invention.

[0004]

Motilin receptors had been known to occur principally in the duodenum but recently it has been shown that they

also occur in the large intestine, or the lower part of the gastrointestinal tract (William et al., Am. J. Physiol., 262, G50-G55 (1992)), and this indicates the possibility that motilin is involved not only in the motility of the upper part of the gastrointestinal tract but also in the motility of its lower part.

[0005]

Reports have also been made of the cases of hypermotilinemia in patients with irritable bowel syndrome who were manifesting diarrhea and in patients with irritable bowel syndrome who were under stress (Preston et al., Gut, 26, 1059-1064 (1985); Fukudo et al., Tohoku J. Exp. Med., 151, 373-385 (1987)) and this suggests the possibility that increased blood motilin levels are involved in the disease. Other diseases that have been reported to involve hypermotilinemia include crohn's disease, ulcerative colitis, pancreatitis, diabetes mellitus, obesity, malabsorption syndrome, bacterial diarrhea, atrophic gastritis and postgastroenterectomy syndrome. The antagonists of motilin receptors have the potential to ameliorate irritable bowel syndrome and other diseased states accompanied by increased blood motilin levels.

[0006]

[Problems to be Solved by the Invention]

An object of the present invention is to provide halogen-substituted benzene derivatives that function as an antagonist of motilin receptors and which are useful as medicines.

[0007]

[Means for Solving the Problem]

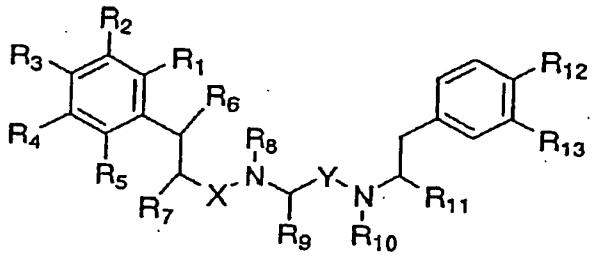
The present inventors conducted repeated intensive studies in an attempt to develop compounds having an outstanding motilin receptor antagonistic action. As a result, they found that halogen-substituted benzene derivatives represented by Formula (1) were an excellent antagonist of motilin receptors. The present invention has been accomplished on the basis of this finding.

[0008]

Thus, the present invention provides compounds of Formula (1):

[0009]

[Chemical Formula 3]



(1)

[0010]

wherein:

R_1, R_2, R_3, R_4 and R_5 are hydrogen, halogen, hydroxy, or amino and at least one of R_1, R_2, R_3, R_4 and R_5 is halogen;

[0011]

R_6 is hydrogen, optionally substituted straight-chained or branched C_{1-3}alkyl, amino or hydroxy;

[0012]

R_7 is hydrogen, optionally substituted straight-

chained or branched C_{1-3}alkyl, optionally substituted amino or hydroxy;

[0013]

R_8 is hydrogen, methyl or ethyl;

[0014]

R_9 is optionally substituted straight-chained or branched C_{1-6}alkyl, C_{3-7}cycloalkyl or optionally substituted phenyl;

[0015]

R_{10} is hydrogen, methyl or ethyl;

[0016]

R_{11} is hydrogen, optionally substituted straight-chained or branched C_{1-3}alkyl, or $-CO-N(R_{14})R_{15}$;

[0017]

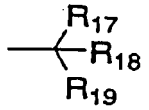
R_{12} is hydroxy or $-OR_{16}$;

[0018]

R_{13} is hydrogen, straight-chained or branched C_{1-6}alkyl, straight-chained or branched C_{2-6}alkenyl, straight-chained or branched C_{2-6}alkynyl or a group of Formula (2):

[0019]

[Chemical Formula 4]



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[0020]

[0021]

R_{14} and R_{15}, which may be the same or different, are hydrogen, optionally substituted straight-chained or

branched C_{1-4}alkyl, or C_{3-7}cycloalkyl, or R_{14} and R_{15}, as $-N(R_{14})R_{15}$, form optionally substituted 3- to 7-membered cyclic amine;

[0022]

R_{16} is straight-chained C_{1-4}alkyl;

[0023]

R_{17} is hydrogen or methyl;

[0024]

R_{18} and R_{19} together form C_{3-7}cycloalkyl or C_{3-7}cycloalkenyl;

[0025]

X is carbonyl or methylene;

[0026]

Y is carbonyl or methylene;

or hydrates or pharmaceutically acceptable salts thereof.

The present invention also provides a medicine containing a compound of Formula (1) as an active ingredient. Further, the present invention provides a motilin receptor antagonist composition containing the compound. The present invention also provides a gastrointestinal motility suppressor agent containing the compound as an active ingredient. Further, the present invention provides a therapeutic of hypermotilinemia containing the compound as an active ingredient.

[0027]

In the definition of the compounds of Formula (1), halogen as R_1, R_2, R_3, R_4 and R_5 is preferably fluorine or chlorine, with fluorine being more preferred. When at least

2 of R_1 to R_5 are halogen, they may be the same or different halogen, however it is preferable that they are the same. The number of halogen atoms is preferably 1 to 3 and more preferably 1 or 2.

[0028]

Preferably, at least one of R_1, R_2, R_3, R_4 and R_5 is halogen and the others are independently hydrogen or hydroxy. Preferably, R_3 is halogen or R_2 and R_3 are the same kind of halogen.

[0029]

Preferred compounds include those in which R_3 is halogen and R_1, R_2, R_4 and R_5 are hydrogen; and those in which R_2 and R_3 are the same halogen and R_1, R_4 and R_5 are hydrogen.

[0030]

The alkyl of the optionally substituted straight-chained or branched C_{1-3}alkyl as R_6 is preferably methyl or ethyl.

[0031]

Exemplary substituents of the optionally substituted straight-chained or branched C_{1-3}alkyl as R_6 include halogen, with fluorine being preferred. The alkyl may have one or more of the above-mentioned substituents, which may be the same or different.

[0032]

The optionally substituted straight-chained or branched C_{1-3}alkyl as R_6 is preferably methyl, ethyl, fluoromethyl or trifluoromethyl, with methyl being

particularly preferred.

[0033]

While R_6 has the definitions set forth above, R_6 is preferably hydrogen or methyl.

[0034]

The alkyl of the optionally substituted straight-chained or branched C_{1-3}alkyl as R_7 is preferably methyl.

[0035]

Exemplary substituents of the optionally substituted straight-chained or branched C_{1-3}alkyl as R_7 include halogen, with fluorine being preferred. The alkyl may have one or more of the above-mentioned substituents, which may be the same or different.

[0036]

The optionally substituted straight-chained or branched C_{1-3}alkyl as R_7 is preferably methyl or trifluoromethyl, with methyl being particularly preferred.

[0037]

Exemplary substituents of the optionally substituted amino as R_7 include straight-chained or branched C_{1-3}alkyl, with methyl and ethyl being preferred. The amino may have one or more of the above-mentioned substituents, which may be the same or different.

[0038]

The optionally substituted amino as R_7 is preferably amino optionally substituted with one or more of the same or different kinds of straight-chained or branched C_{1-3}alkyl; specific examples include amino, methylamino, dimethylamino

and ethylamino, with amino and methylamino being particularly preferred.

[0039]

While R_7 has the definitions set forth above, R_7 is preferably hydrogen or optionally substituted amino, with hydrogen, amino and methylamino being particularly preferred.

[0040]

R_8 is preferably hydrogen or methyl.

[0041]

The alkyl of the optionally substituted straight-chained or branched C_{1-6}alkyl as R_9 is preferably straight-chained or branched C_{1-5}alkyl, e.g., methyl, ethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, 3-pentyl and neopentyl.

[0042]

Exemplary substituents of the optionally substituted straight-chained or branched C_{1-6}alkyl as R_9 include substituted or unsubstituted phenyl (e.g., phenyl, tolyl, para-hydroxyphenyl and para-fluorophenyl), C_{3-7}cycloalkyl, and halogen, with phenyl, cyclohexyl and halogen (particularly fluorine) being preferred.

[0043]

The optionally substituted straight-chained or branched C_{1-6}alkyl as R_9 is preferably methyl, isopropyl, isobutyl, sec-butyl, tert-butyl, 3-pentyl, neopentyl, 1,1,1,3,3,3-hexafluoro-2-propyl, benzyl, para-hydroxybenzyl, phenethyl or cyclohexylmethyl.

[0044]

The C_{3-7}cycloalkyl as R_9 is preferably cyclopentyl or cyclohexyl.

[0045]

Exemplary substituents of the optionally substituted phenyl as R_9 include hydroxy, amino, methyl, ethyl and halogen. The phenyl may have one or more of the above-mentioned substituents, which may be the same or different.

[0046]

The optionally substituted phenyl as R_9 is preferably phenyl.

[0047]

While R_9 has the definitions set forth above, R_9 is preferably methyl, isopropyl, isobutyl, sec-butyl, tert-butyl, 3-pentyl, neopentyl, 1,1,1,3,3,3-hexafluoro-2-propyl, cyclohexyl, phenyl, benzyl, para-hydroxybenzyl, phenethyl or cyclohexylmethyl, with isopropyl being particularly preferred.

[0048]

R_{10} is preferably hydrogen or methyl.

[0049]

The alkyl of the optionally substituted straight-chained or branched C_{1-3}alkyl as R_{11} is preferably methyl.

[0050]

Exemplary substituents of the optionally substituted straight-chained or branched C_{1-3}alkyl as R_{11} include amino optionally substituted with one or more of the same or different kind of straight-chained or branched C_{1-3}alkyl (e.g., amino, methylamino, dimethylamino and ethylamino),

optionally substituted 3- to 7-membered cyclic amino (exemplary substituents of the cyclic amino include hydroxy, amino, carboxyl, carbamoyl and methyl), hydroxy, methoxy, halogen, with amino, and hydroxy being preferred. The alkyl may have one or more of the above-mentioned substituents, which may be the same or different.

[0051]

The optionally substituted straight-chained or branched C_{1-3}alkyl as R_{11} is preferably methyl, aminomethyl, and hydroxymethyl, with methyl being particularly preferred.

[0052]

The alkyl of the optionally substituted straight-chained or branched C_{1-4}alkyl as R_{14} and R_{15} of -CO-N(R_{14})R_{15} as R_{11} is preferably methyl, ethyl, propyl, isopropyl, isobutyl, or sec-butyl, with methyl being more preferred.

[0053]

Exemplary substituents of the optionally substituted straight-chained or branched C_{1-4}alkyl as R_{14} and R_{15} in -CO-N(R_{14})R_{15} as R_{11} include optionally substituted straight-chained or branched C_{1-3}alkoxy (exemplary substituents of the optionally substituted straight-chained or branched C_{1-3}alkoxy include hydroxy, amino, carboxyl and carbamoyl), hydroxy, amino, methylamino, dimethylamino and carbamoyl, with hydroxy and methoxy being preferred.

[0054]

Examples of the optionally substituted straight-chained or branched C_{1-4}alkyl as R_{14} and R_{15} in -CO-N(R_{14})R_{15} as R_{11} include methyl, ethyl, hydroxymethyl, methoxymethyl,

2-hydroxyethyl, 2-aminoethyl, 2-hydroxy-2-methylpropyl, 2-hydroxy-2-methylpropyl, and 2-amino-2-methylpropyl, with methyl, ethyl, hydroxymethyl, and methoxymethyl being preferred.

[0055]

The C_{3-7}cycloalkyl as R_{14} and R_{15} in $-CO-N(R_{14})R_{15}$ as R_{11} is preferably cyclopropyl.

[0056]

The 3- to 7-membered cyclic amine of the optionally substituted 3- to 7-membered cyclic amine as $-N(R_{14})R_{15}$ as R_{11} include aziridine, azetidine, pyrrolidine, piperidine, piperazine and morpholine, with piperazine and morpholine being preferred. Exemplary substituents of the optionally substituted 3- to 7-membered cyclic amine include hydroxy, amino, carboxyl and methyl.

[0057]

The $-CO-N(R_{14})R_{15}$ as R_{11} is preferably carbamoyl, methylcarbamoyl, ethylcarbamoyl, and hydroxymethylcarbomoyl, methoxymethylcarbamoyl, with carbamoyl being more preferred.

[0058]

While R_{11} has the definitions set forth above, R_{11} is preferably methyl, aminomethyl, hydroxymethyl, carbamoyl, methylcarbamoyl, hydroxymethylcarbamoyl, and methoxymethyl-carbamoyl, with methyl and carbamoyl being more preferred.

[0059]

The straight-chained C_{1-4}alkyl as R_{16} of $-OR_{16}$ as R_{12} is preferably methyl.

[0060]

R_{12} is preferably hydroxy.

[0061]

The straight-chained or branched C_{1-6}alkyl as R_{13} is preferably straight-chained or branched C_{2-5}alkyl, more preferably branched C_{3-5}alkyl, and most preferably tert-butyl.

[0062]

The straight-chained or branched C_{2-6}alkenyl as R_{13} is preferably straight-chained or branched C_{3-5}alkenyl and more preferably branched C_{3-5}alkenyl.

[0063]

The straight-chained or branched C_{2-6}alkynyl as R_{13} is preferably straight-chained or branched C_{3-5}alkynyl and more preferably branched C_{3-5}alkynyl.

[0064]

R_{17} in Formula (2) as R_{13} is preferably methyl.

[0065]

The C_{3-7}cycloalkyl formed by R_{18} and R_{19} in Formula (2) as R_{13} is preferably C_{3-5}cycloalkyl.

[0066]

The C_{3-7}cycloalkenyl formed by R_{18} and R_{19} in Formula (2) as R_{13} is preferably C_{3-5}cycloalkenyl.

[0067]

While R_{13} has the definitions set forth above, R_{13} is preferably isopropyl, tert-butyl, 1,1-dimethylpropyl and 1,1-dimethyl-2-propenyl, with tert-butyl being more preferred.

[0068]

X is preferably carbonyl or methylene.

[0069]

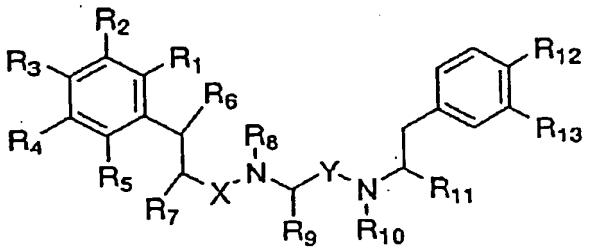
Y is preferably carbonyl or methylene.

[0070]

Examples of compounds of Formula (1)

[0071]

[Chemical Formula 5]



(1)

[0072]

wherein:

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, X and Y are as defined as above

include those compounds in which at least one of R_1, R_2, R_3, R_4 and R_5 is halogen and the others are hydrogen or hydroxy; R_6 is hydrogen or methyl; R_7 is hydrogen or optionally substituted amino; R_8 is hydrogen or methyl; R_9 is methyl, isopropyl, isobutyl, sec-butyl, tert-butyl, 3-pentyl, neopentyl, 1,1,1,3,3,3-hexafluoro-2-propyl, cyclohexyl, phenyl, benzyl, phenethyl, para-hydroxybenzyl or cyclohexylmethyl; R_{10} is hydrogen or methyl; R_{11} is methyl, carbamoyl, methylcarbamoyl, or dimethylcarbamoyl; R_{12} is hydroxy; R_{13} is isopropyl, tert-butyl (tBu), 1,1-dimethylpropyl or 1,1-dimethyl-2-propenyl. More preferred compounds are Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2, Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2, and Phe(3,4-F_2)-N-Me-Val-

N-Me-Tyr(3-tBu)-NH_2, with Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 being particularly preferred.

[0073]

Salt-forming acids include inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and phosphoric acid, as well as organic acids such as acetic acid, oxalic acid, maleic acid, fumaric acid, citric acid, succinic acid, tartaric acid, methanesulfonic acid and trifluoroacetic acid.

[0074]

The compounds of the present invention can occur as optical isomers and the respective optical isomers and mixtures thereof are all included within the scope of the invention.

[0075]

The compounds of the present invention can also be obtained as hydrates.

[0076]

On the pages that follow, the present invention is described more specifically and the amino acids that constitute peptides, the amino acids protected by protecting groups, the protecting groups and reagents are represented by the following abbreviations:
Val: valine, Phe: phenylalanine, Tyr: tyrosine, Z: benzyloxycarbonyl, Boc: tert-butoxycarbonyl, CMPI: 2-chloro-1-methylpyridinium iodide, PyCIU: chloro-N,N,N',N'-bis(tetramethylene)formamidinium hexafluorophosphate, DIC: N,N'-diisopropylcarbodiimide, HOBT: 1-hydroxylbenzotriazole

monohydrate, NMM: N-methylmorpholine, TEA: triethylamine, DIEA: diisopropylethylamine, TFA: trifluoroacetic acid, THF: tetrahydrofuran, DMF: N,N-dimethylformamide.

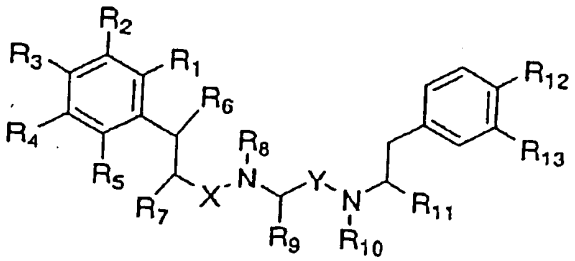
[0077]

[Mode for Carrying Out the Invention]

The compounds of Formula (1)

[0078]

[Chemical Formula 6]



(1)

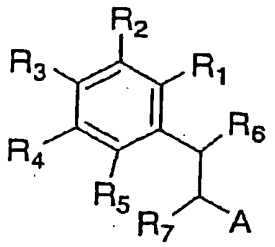
[0079]

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, X and Y are as defined above

can basically be produced by binding Compound (I), Compound (II) and Compound (III), which are represented by the following formulae and in which functional groups other than those involved in bond formation are protected as required:

[0080]

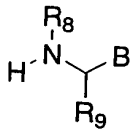
[Chemical Formula 7]



(I)

[0081]

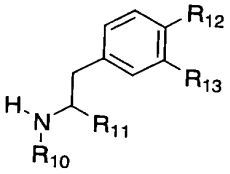
[Chemical Formula 8]



(II)

[0082]

[Chemical Formula 9]



(III)

[0083]

A and B in Formulae (I) to (III) are functional groups which can form a bond by the reaction with amino; specific examples are carboxyl, formyl, halomethylene of which halogen is chlorine, bromine or iodine, and sulfonyloxymethylene of which sulfonyl is methanesulfonyl, trifluoromethanesulfonyl, paratoluenesulfonyl and the like. R_1 to R_{10}, R_{12} and R_{13} are as defined above, provided that when they are reactive groups such as amino, hydroxy or carboxyl, they are protected by normally used appropriate protecting groups, if desired. R_{11} is as defined above or is a functional group which is convertible to one of the above defined groups.

[0084]

The compounds of Formula (1) may be produced by first binding Compound (II) and Compound (III), optionally followed by deprotection, and then binding the resultant

compound with Compound (I), optionally followed by deprotection or conversion of the functional group(s). Alternatively, the compound of Formula (1) may be produced by first binding Compound (I) and Compound (II), optionally followed by deprotection, and then binding the resultant compound with Compound (III), optionally followed by deprotection or conversion of the functional group(s).

[0085]

The compounds of the present invention may be produced by either the solid-phase process or the liquid-phase process. In the production by the solid-phase process, an automatic organic synthesizer can be used but it may be replaced by the manual procedure.

[0086]

Almost all amino acids that are used for the production of the compounds of the present invention are commercially available and readily purchasable. Those which are not commercially available can be produced by well-known established methods such as the Strecker synthesis, the Bucherer method, the acetamido malonic ester method, the method of alkylating an amino group protected glycine ester and the Z-α-phosphonoglycine trimethylester method.

[0087]

Compound (I), if it has a functional group such as amino and hydroxy, with the functional group being protected, is carboxylic acid (A is $-CO_2H$), aldehyde (A is -CHO), alkylhalide (A is $-CH_2$-Hal), sulfonate (A is $-CH_2-OSO_2R$) or the like. In this case, bond can be formed by

reacting A of Compound (I) with the amino group of Compound (II).

[0088]

Compound (II) can, in almost all cases, be derived from an α-amino acid and B is carboxyl ($-CO_2H$), formyl (-CHO), halomethyl ($-CH_2$-Hal), sulfonyloxymethyl (RSO_2O-CH_2-) or the like. The amino group of Compound (II) is reacted with A of Compound (I) to form bond and B of Compound (II) is reacted with the amino group of Compound (III) to form bond.

[0089]

Compound (III) is an ethylamine derivative and can be generally derived from an amino acid. The amino group of Compound (III) is reacted with B of Compound (II) to form bond.

[0090]

When A or B is carboxyl, various methods known in peptide synthesis may be used to activate the carboxyl for condensation with the amino group and such methods include the use of benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP), the use of PyCIU, the use of bromo tripyrrolidino phosphonium hexafluorophosphate (PyBrop), the use of chlorotripyrrolidino phosphonium hexafluorophosphate (PyClop), the use of O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), the use of DIC, the use of N-ethyl-N'-3-dimethylaminopropyl carbodiimide (WSCI), the use of dicyclohexyl carbodiimide

(DCC), the use of diphenylphosphorylazide (DPPA), the use of CMPI, the use of 2-bromo-1-methylpyridinium iodide (BMPI), the combination of one of these reagents with HOBT or N-hydroxysuccinimide (HONSu), the mixed acid anhydride method using isobutyl chloroformate or the like, the method of changing the carboxyl group to a pentafluorophenyl ester (OPfp), a p-nitrophenyl ester (ONP) or an N-hydroxysuccinimide ester (OSu), and the combination of one of these methods with HOBT. If necessary, a base such as TEA, DIEA, NMM or 4-dimethylaminopyridine (DMAP) may be added to accelerate the reaction.

[0091]

When A or B is formyl, bond can be formed by conventional reductive bond forming reaction with amino group. When A or B is halomethylene or sulfonyloxymethylene, bond can be formed by substitution reaction with amino group.

[0092]

The compounds of the present invention can also be produced by applying the specific methods of production to be described in the following Examples.

[0093]

[Examples]

On the pages that follow, the production of the compounds of the invention is described more specifically by reference to Examples, to which the invention is by no means limited.

[0094]

In order to demonstrate the utility of the compounds of the invention, typical examples of them were subjected to pharmacological tests on the motilin receptor antagonistic action and the results are described under Test Examples. The chemical structural formulae or chemical names of the compounds produced in Examples are set forth in Tables A-1 and A-2.

[0095]

[Table 1]

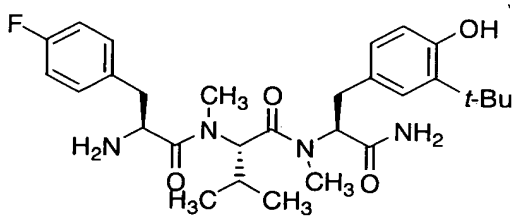
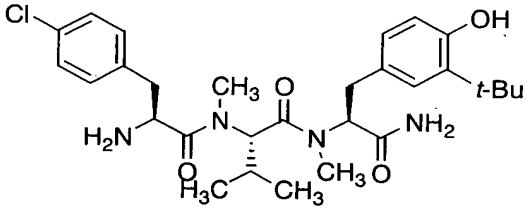
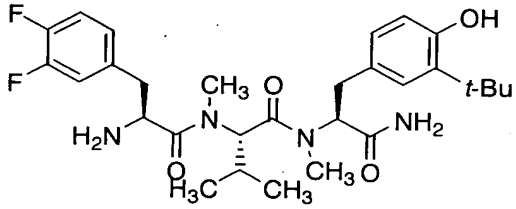
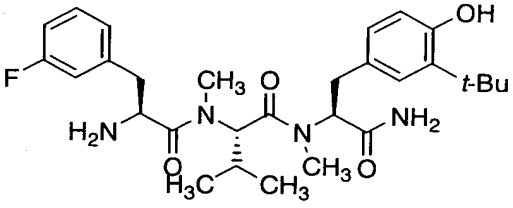
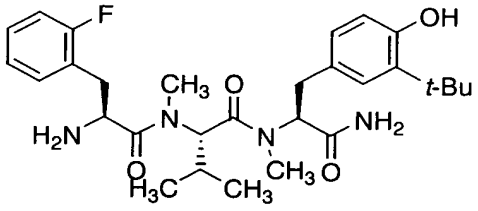
Table A-1

Example No.	Structural formula or chemical name
1	Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2
2	Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2
3	Phe(3,4-F_2)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2
4	Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2
5	Phe(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

[0096]

[Table 2]

Table A-2

Example No.	Structural formula
1	
2	
3	
4	
5	

[0097]

In the following Examples, mass spectra (EI-MS) were taken by SHIMADZU GCMS-QP5050A or SHIMADZU GCMS-QP1000.

[0098]

NMR was taken by JEOL JNM-EX-270 (270 MHz).

[0099]

Example 1

Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

(1) Synthesis of Tyr(3-tBu)-OMe

To a solution of Tyr-OMe·HCl (500 g, 2.16 mol) in tert-butyl acetate (4500 ml), 70% $HClO_4$ (278 ml, 3.24 mol) was added and stirred for 4.5 days at room temperature. The reaction mixture was evaporated under reduced pressure; the thus obtained residue was dissolved in ethyl acetate, poured into a saturated aqueous $NaHCO_3$ solution and stirred. The organic layer was collected and washed with a saturated aqueous $NaHCO_3$ solution and saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was mixed with ether (950 ml) and at room temperature, stirred overnight. The thus precipitated crystals were collected by filtration to give Tyr(3-tBu)-OMe (242 g, 45%).

^{1}H-NMR($CDCl_3$): δ 1.38(9H,s), 2.83(1H,dd,J=13.7,7.4Hz), 3.02(1H,dd,J=13.7,5.1Hz), 3.70(1H,dd,J=7.4,5.1Hz), 3.73(3H,s), 6.55(1H,d,J=7.9Hz), 6.85(1H,dd,J=7.9,1.7Hz), 7.04(1H,d,J=1.7Hz)

(2) Synthesis of Z-Tyr(3-t-Bu)-OMe

To a solution of Tyr(3-tBu)-OMe (41.4 g, 0.165 mol)

in 1,4-dioxane (170 ml) and H_2O (170 ml), under cooling with ice, sodium carbonate (26.2 g, 0.247 mol) was added and then Z-Cl (24.7 ml 0.173 mol) was further added over 25 min., followed by stirring for 2.5 hours at room temperature. The reaction mixture was mixed with water, extracted with chloroform, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus precipitated crystals were collected by filtration, washed with n-hexane and dried to give Z-Tyr(3-t-Bu)-OMe (54.7 g, 86%).

^{1}H-NMR($CDCl_3$): δ 1.36(9H,s), 3.04(2H,brd,J=5.6Hz), 3.72(3H,s), 4.57-4.68(1H,m), 4.97(1H,brs), 5.10(2H,s), 5.20(1H,brd,J=7.9Hz), 6.55(1H,d,J=7.9Hz), 6.78(1H,dd,J=7.9,2.0Hz), 6.95(1H,d,J=2.0Hz), 7.26-7.41(5H,m)

(3) Synthesis of Z-Phe(3-tBu-4-benzyloxy)-OMe

A solution of Z-Tyr(3-tBu)-OMe (1.0 g, 2.60 mmol), benzyl bromide (0.56 ml, 4.68 mmol) and potassium carbonate (1.08 g, 7.79 mmol) in DMSO (5 ml) was stirred overnight. The resulting mixture was mixed with a saturated aqueous ammonium chloride solution, extracted with ethyl acetate. The organic layer was washed with water and then saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:5) to give Z-Phe(3-tBu-4-benzyloxy)-OMe (1.44 g, 99%).

^{1}H-NMR($CDCl_3$): δ 1.36(9H,s), 3.05(2H,d,J=5.6Hz), 3.71(3H,s), 4.60-4.68(1H,m), 5.06(2H,s), 5.09(2H,s), 5.24(1H,brd,J=8.3Hz), 6.82(1H,d,J=8.5Hz), 6.88(1H,dd,J=8.5,1.8Hz), 7.00(1H,d,J=1.8Hz), 7.27-7.50(10H,m)

(4) Synthesis of Z-N-Me-Phe(3-tBu-4-benzyloxy)-NH_2

To a solution of Z-Phe(3-tBu-4-benzyloxy)-OMe (1.44 g, 2.60 mmol) in 1,4-dioxane (30 ml), a 2N aqueous sodium hydroxide solution (3 ml) was added and stirred for 2 hours. The resulting mixture was mixed with water and washed with ethyl acetate; the aqueous layer was rendered acidic by the addition of dilute hydrochloric acid and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure, giving crude Z-Phe(3-tBu-4-benzyloxy)-OH (1.35 g).

To a solution of the thus obtained crude Z-Phe(3-tBu-4-benzyloxy)-OH (1.35 g) in THF (7 ml), under cooling with ice, methyl iodide (1.3 ml, 20.8 mmol) was added and then sodium hydride (60% in oil, 312 mg, 7.8 mmol) was added slowly, followed by stirring for 21 hours at room temperature. The resulting mixture was mixed with water, rendered acidic by the addition of dilute hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure, giving crude Z-N-Me-Phe(3-tBu-4-benzyloxy)-OH (1.60 g).

To a solution of the thus obtained crude Z-N-Me-Phe(3-tBu-4-benzyloxy)-OH (1.60 g) in THF (25 ml), under cooling with ice, ethyl chloroformate (0.27 ml, 2.86 mmol) and NMM (0.31 ml, 2.86 mmol) were added in that order. The mixture was stirred for 15 min. and further stirred for another 15 min. while bubbling gaseous ammonia therein. The resultant mixture was left standing at room temperature, diluted with ethyl acetate and washed with water and then saturated brine. The organic layer was dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 2:1) to give Z-N-Me-Phe(3-tBu-4-benzyloxy)-NH_2 (1.08 g, 88%, in 3 steps).

^{1}H-NMR($CDCl_3$): δ 1.37(9H,s), 2.87(3H,s), 2.86-2.99(1H,m), 3.21-3.35(1H,m), 4.73-4.95(1H,m), 5.06(2H,s), 5.09(2H,s), 5.67,5.83 and 6.13(3/2H,brs), 6.78-7.47(27/2H,m)

(5) Synthesis of N-Me-Tyr(3-tBu)-NH_2

To a solution of Z-N-Me-Phe(3-tBu-4-benzyloxy)-NH_2 (1.08 g, 2.28 mmol) in methanol (20 ml), 10% palladium/carbon (100 mg) was added and stirred in a hydrogen atmosphere at room temperature overnight. The mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1) to give N-Me-Tyr(3-tBu)-NH_2 (0.55 g, 96%).

^{1}H-NMR($CDCl_3$): δ 1.40(9H,s), 2.31(3H,s),

2.63(1H,dd,J=14.7,10.7Hz), 3.10-3.19(2H,m), 5.24(1H,brs), 5.38(1H,brs), 6.63(1H,d,J=7.9Hz), 6.91(1H,dd,J=7.9,1.8Hz), 7.05(1H,brs), 7.10(1H,d,J=1.8Hz)

(6) Synthesis of Z-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

To a solution of Z-N-Me-Val-OH (700 mg, 2.64 mmol), N-Me-Tyr(3-tBu)-NH_2 (0.55 g, 2.20 mmol) and CMPI (674 mg 2.64 mmol) in THF (22 ml), under cooling with ice, TEA (0.61 ml) was added and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 3:2) to give Z-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.98 g, 90%).

^{1}H-NMR($CDCl_3$):(four rotamers) δ 0.07, 0.32, 0.63, 0.74, 0.79, 0.81, 0.84 and 0.89(6H,d,J=6.3-6.6Hz), 1.30, 1.33, 1.37 and 1.39(9H,s), 2.13-2.33(1H,m), 2.34, 2.41, 2.78, 2.87 and 2.98(6H,s), 2.79-3.22(2H,m), 4.40 and 4.32(1H,d,J=10.6Hz), 4.60-5.43(5H,m), 5.96(1H,brs), 6.23-7.12(3H,m), 7.26-7.47(5H,m)

(7) Synthesis of N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (Intermediate I-b3 in the following Tables)

A mixture of Z-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.98 g, 1.97 mmol) and 20% palladium hydroxide/carbon (0.10 g) in methanol (20 ml) was stirred at room temperature in a hydrogen atmosphere for 1.5 hours. The reaction mixture was

filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1) to give N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.71 g, 99%).

^{1}H-NMR($CDCl_3$):(two rotamers) δ 0.35,0.71,0.92 and 0.96(6H,d,J=6.9Hz), 1.36 and 1.37(9H,s), 1.73-1.81 and 2.03-2.17(1H,m), 1.74 and 2.23(3H,s), 2.64(1H,d,J=9.2Hz), 2.90-3.04(1H,m), 2.93 and 3.00(3H,s), 3.19 and 4.60(1H,dd,J=14.7,5.8 and 10.7,3.8Hz), 5.29,5.32 and 6.06(2H,brs), 5.59(1H,dd,J=10.4,5.8Hz), 6.54 and 6.60(1H,d,J=7.9Hz), 6.79 and 6.93(1H,dd,J=7.9,2.0 and 1.7Hz), 7.01 and 7.07(1H,d,J=2.0 and 1.7Hz), 8.10(1H,brs)

(8) Synthesis of Z-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

To a solution of Z-Phe(4-F)-OH (1.09 g, 3.44 mmol), N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (1.04 g, 2.87 mmol) and CMPI (878 mg, 3.44 mmol) in THF (30 ml), TEA (0.96 ml, 6.88 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: n-hexane:ethyl acetate =1:3) to give Z-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (1.73 g, 91%).

^{1}H-NMR($CDCl_3$):(two rotamers) δ 0.57,0.73,0.75 and 0.90(6H,d,J=6.3-6.6Hz), 1.33 and 1.39(9H,s), 2.18-

3.43(5H,m), 2.40 and 3.03(3H,s), 2.74 and 3.01(3H,s), 4.62-5.49(7H,m), 5.95(1H,brs), 6.44(1H,d,J=7.9Hz), 6.57-7.35(12H,m)

(9) Synthesis of Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

A mixture of Z-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (1.73 g, 2.61 mmol) and 10% palladium/carbon (340 mg) in methanol (50 ml) was stirred at room temperature in a hydrogen atmosphere for 17 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1) to give Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (1.25 g, 91%).

EI-MS:528(M^+)

^{1}H-NMR($CDCl_3$):(two rotamers) δ 0.50,0.76,0.79 and 0.93(6H,d,J=6.3-6.9Hz), 1.34 and 1.39(9H,s), 2.19-2.95(5H,m), 2.50 and 3.03(3H,s), 2.81 and 3.02(3H,s), 3.17 and 3.34(1H,dd,J=15.2,5.9 and 13.9,6.9Hz), 3.66 and 3.84(1H,dd,J=8.9,4.6 and 8.6,4.6Hz), 4.91 and 5.07(1H,d,J=10.6Hz), 5.07,5.19,5.30,5.98 and 6.64(2H,brs), 5.49(1H,dd,J=10.6,5.9Hz), 6.35 and 6.62(1H,d,J=7.9Hz), 6.74(2/3H,dd,J=7.9,1.7Hz), 6.95-7.11(19/3H,m)

[0100]

Example 2

Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

(1) Synthesis of Boc-Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

To a solution of Boc-Phe(4-Cl)-OH (354 mg, 1.18 mmol), N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.33 g, 0.908 mmol) and CMPI

(301 mg, 1.18 mmol) in THF (8 ml), TEA (0.38 ml, 2.72 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 40:1:0.05) to give Boc-Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.45 g, 77%).

(2) Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

To a solution of Boc-Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.45 g, 0.697 mmol) in methylene chloride (4 ml), TFA (3 ml) was added, stirred for 20 min. and evaporated to remove the solvent under reduced pressure. The thus obtained residue was mixed with a saturated aqueous $NaHCO_3$ solution, and extracted with methylene chloride. The organic layer was dried over anhydrous sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 30:1:0.1) to give Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (355 mg, 93%).

EI-MS:544 and 546(M^+)

^{1}H-NMR($CDCl_3$):(two rotamers) δ 0.49,0.75,0.78 and 0.93(6H,d,J=6.3-6.9Hz), 1.34 and 1.38(9H,s), 2.10-2.92(5H,m), 2.50 and 3.04(3H,s), 2.80 and 3.01(3H,s), 3.13

and 3.33(1H,dd,J=15.2,5.9 and 13.9,6.9Hz), 3.67 and 3.85(1H,dd,J=8.9,5.0 and 8.6,5.0Hz), 4.90 and 5.06(1H,d,J=10.6Hz), 5.33,5.41, 5.99 and 6.61(2H,brs), 5.49(1H,dd,J=10.6,5.9Hz), 6.37 and 6.63(1H,d,J=7.9Hz), 6.72 and 6.98(1H,dd,J=7.9,1.7Hz), 7.07-7.10(3H,m), 7.25-7.31(2H,m)

[0101]

Example 3

Phe(3,4-F_2)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

(1) Synthesis of Fmoc-Phe(3,4-F_2)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

To a solution of Fmoc-Phe(3,4-F_2)-OH (500 mg, 1.18 mmol), N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.33 g, 0.908 mmol) and CMPI (301 mg, 1.18 mmol) in THF (8 ml), TEA (0.38 ml, 2.72 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 60:1:0.05), giving Fmoc-Phe(3,4-F_2)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.56 g, 80%).

(2) Synthesis of Phe(3,4-F_2)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

To a solution of Fmoc-Phe(3,4-F_2)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.55 g, 0.715 mmol) in methylene chloride (5 ml), diethylamine (5 ml) was added, stirred for 4 hours

and then evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:ethanol:aqueous ammonia = 60:1:0.1) to give Phe(3,4-F_2)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (381 mg, 97%).

EI-MS:546(M^+)

^{1}H-NMR($CDCl_3$):(two rotamers) δ 0.51,0.74,0.79 and 0.93(6H,d,J=6.3-6.9Hz), 1.33 and 1.38(9H,s), 2.10-2.93(5H,m), 2.51 and 3.03(3H,s), 2.83 and 3.01(3H,s), 3.17 and 3.33(1H,dd,J=14.8,5.9 and 13.9,6.6Hz), 3.66 and 3.84(1H,dd,J=8.4,5.0 and 8.6,4.3Hz), 4.88 and 5.07(1H,d,J=10.6Hz), 5.41, 5.9(1H,brs), 5.41-5.51(1H,m), 6.43 and 6.64(1H,d,J=7.9Hz), 6.75(2/5H,dd,J=7.9,1.7Hz), 6.84-7.16(28/5H,m)

[0102]

Example 4

Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

(1) Synthesis of Boc-Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

To a solution of Boc-Phe(3-F)-OH (0.20 g, 0.706 mmol), N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.21 g, 0.578 mmol) and CMPI (0.20 g, 0.783 mmol) in THF (6 ml), TEA (0.30 ml, 2.15 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing

solvent: chloroform:methanol:aqueous ammonia = 60:1:0.05) to give Boc-Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.33 g, 91%).

(2) Synthesis of Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

To a solution of Boc-Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.33 g, 0.525 mmol) in methylene chloride (3 ml), TFA (1.5 ml) was added, stirred for 15 min. and then evaporated to remove the solvent under reduced pressure. The residue was mixed with methylene chloride, washed with a saturated aqueous $NaHCO_3$ solution, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 40:1:0.1) to give Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (241 mg, 87%).

EI-MS:528(M^+)

^{1}H-NMR($CDCl_3$):(two rotamers) δ 0.51,0.73,0.78 and 0.93(6H,d,J=6.3-6.6Hz), 1.33 and 1.38(9H,s), 2.10-2.96(5H,m), 2.46 and 3.03(3H,s), 2.78 and 3.01(3H,s), 3.16 and 3.35(1H,dd,J=14.8,5.9 and 13.9,6.6Hz), 3.70 and 3.90(1H,dd,J=8.3,5.6 and 8.6,5.0Hz), 4.89 and 5.06(1H,d,J=10.6Hz), 5.42, 5.99(1H,brs), 5.43-5.52(1H,m), 6.41 and 6.64(1H,d,J=7.9Hz), 6.72(2/5H,dd,J=7.9,1.7Hz), 6.83-6.99(18/5H,m), 7.10(2/5H,d,J=1.7Hz), 7.22-7.33(1H,m)

[0103]

Example 5

Phe(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

(1) Synthesis of Boc-Phe(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

To a solution of Boc-Phe(2-F)-OH (0.20 g, 0.706 mmol), N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.21 g, 0.578 mmol) and CMPI (0.20 g, 0.783 mmol) in THF (6 ml), TEA (0.30 ml, 2.15 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 60:1:0.05) to give Boc-Phe(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.33 g, 91%).

(2) Synthesis of Phe(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

To a solution of Boc-Phe(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.33 g, 0.525 mmol) in methylene chloride (3 ml), TFA (1.5 ml) was added, stirred for 15 min. and then evaporated to remove the solvent under reduced pressure. The residue was mixed with methylene chloride, washed with a saturated aqueous $NaHCO_3$ solution, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 40:1:0.1) to give Phe(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (235 mg, 85%).

EI-MS:528(M^+)

^{1}H-NMR($CDCl_3$):(two rotamers) δ 0.45,0.71,0.79 and 0.93(6H,d,J=5.9-6.6Hz), 1.31 and 1.38(9H,s), 2.10-

2.89(5H,m), 2.47 and 3.06(3H,s), 2.76 and 3.01(3H,s), 3.14 and 3.34(1H,dd,J=14.3,5.9 and 13.9,6.6Hz), 3.79 and 3.95(1H,dd,J=8.4,5.0 and 8.6,4.3Hz), 4.88 and 5.06(1H,d,J=10.6Hz), 5.37, 5.99(1H,brs), 5.41-5.51(1H,m), 6.43(3/5H,d,J=7.9Hz), 6.56(2/5H,brs), 6.60-6.71(1H,m), 6.92-7.29(6H,m)

[0104]

Test Example 1

Motilin receptor binding test

A motilin receptor binding test was conducted in the following manner [Vantrappen et al., Regul. Peptides, 15, 143 (1986)]. The duodenum was extracted from a slaughtered rabbit, had the mucous membrane separated and homogenized in 50 mM Tris buffer to prepare a protein sample. The protein sample was incubated together with ^{125}I motilin 25 pM and thereafter the radioactivity bound to the protein was measured. Specific binding was defined as the difference between the radioactivity in the case of adding a great excess amount of motilin (10^{-7} M) and that in the case of no adding. The activity of the compound was expressed by IC_{50} (in nM), as the concentration sufficient to reduce the specific binding by 50%. Result is shown in Table B-1.

[0105]

Test Example 2

Action on the contraction of a specimen of longitudinal muscle in the duodenum extracted from a rabbit

The action on the motilin-induced contraction of a specimen of longitudinal muscle in the duodenum extracted

from a rabbit was investigated by the following method. A duodenum specimen (5 x 15 mm) extracted from a slaughtered rabbit was suspended in an organ bath (10 ml) such that the longitudinal muscle would run vertically; the bath was filled with a Krebs solution kept at 28°C. A mixed gas (95% O_2 and 5% CO_2) was continuously bubbled into the Krebs solution and the contraction of the duodenum specimen was recorded isotonically (with a 1-g load) via an isotonic transducer (ME-3407, ME Commercial, Tokyo, Japan). The degree of contraction was expressed in relative values, with the contraction by acetylcholine at a dose of 10^{-4} M being taken as 100%. The activity of the compound was calculated as pA_2 value indicating its effect on the dose-dependent muscle contraction by the motilin put into the organ bath. The result is shown in Table B-1.

[0106]

[Table 3]

Table B-1

Example No.	Motilin receptor binding test, IC_{50} (nM)	Contraction suppressing test, pA_2
1	0.89	8.8

[0107]

[Advantages]

The compounds of the present invention function as a motilin receptor antagonist and are useful as medicines including therapeutics of irritable bowel syndrome.

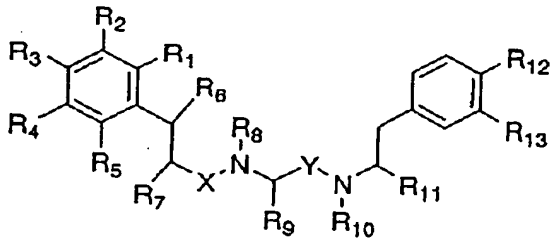
[Name of Document] Abstract

[Abstract]

[Problem] The present invention has as its object providing halogen-substituted benzene derivatives that function as a motilin receptor antagonist and which are useful as medicines.

[Means for Solving] The invention provides compounds of Formula (1):

[Chemical Formula 10]



(1)

wherein:

R_1, R_2, R_3, R_4 and R_5 are hydrogen, halogen, etc. and at least one of R_1, R_2, R_3, R_4 and R_5 is halogen;

R_6 is alkyl, etc.;

R_7 is amino, etc.;

R_8 is methyl, etc.;

R_9 is alkyl, etc.;

R_{10} is methyl, etc.;

R_{11} is alkyl, etc.;

R_{12} is hydroxy, etc.;

R_{13} is alkyl, etc.:

X is carbonyl, etc.;

Y is carbonyl, etc.;

or a hydrate or pharmaceutically acceptable salt thereof.

[Advantages] The compounds of the above Formula (1) function as a motilin receptor antagonist and are useful as medicines.

[Selected Drawing] None